Clinical Education Initiative
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TITLE: OPTIMIZING BONE HEALTH IN THE HIV PATIENT

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Optimizing Bone Health in the HIV Patient
[video transcript]

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- [Jim] Welcome to Physicians' Research Network. I'm Jim Braun, the Course Director of the monthly meetings of PRN in New York City. Since our beginning in 1990, PRN has been committed to enhancing the skills of our members in the diagnosis, management, and prevention of HIV disease, as well as its co-infections and complications.

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We hope this recording of Todd Brown's presentation, Optimizing Bone Health in the HIV-infected Patient, will be helpful to you in your daily practice, and I invite you to join us in New York City for our live meetings in the future.

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PRN is a not for profit organization dedicated to peer support and education for physicians, nurse practitioners, and physician assistants. A membership is open to all interested clinicians nationwide at our website prn.org, and now, allow me to introduce

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Todd Brown, Associate Professor of Medicine and Epidemiology in the Division of Endocrinology, Diabetes, and Metabolism at the Johns Hopkins University in Baltimore, Maryland.

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- Thanks for inviting me back. It's always good to speak to you. I think last year I talked about testosterone, so I'll talk about one of my, another one of my favorite endocrine topics, which is bone.

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So what I want to do today is to have you all understand risk factors for bone loss in HIV-infected patients and to know how to manage antiretroviral therapy to minimize the impact to bone and also to be aware of other treatments to improve bone health in HIV-infected patients and also their risks and benefits.

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So osteoporosis is really one of the quintessential diseases of aging, and this slide shows what bone does

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over the course of someone's lifetime. So we all reach our peak bone mass somewhere around between ages 20 and 30, generally around age 25 or so. And then it's, we stay stable for a little while, and it's downhill after about age 40. Men have a slower decline in bone mineral density, whereas women have a steeper decline with menopause. Now peak bone mass is really important. Now peak bone mass is a major determinant of someone's bone mineral density when they're 65 or 70 when the fracture risk increases, and this is a really important question in pediatric populations, including pediatric HIV, which I don't have time to talk about, which, but is really important. But you get this drop in bone mineral density, And this drop in bone mineral density is important because it predisposes people to fracture,

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and fracture of course is one of the major problems with aging, and so after about age 65 in women if I can get my, 65 in women and about 70 in men, there is an exponential increase in fracture risk, and so fractures are a problem for a few reasons.

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So they're, of course, it's a big cause of morbidity and healthcare costs, but it's also a big cause of mortality, and so here's some data

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It's a meta-analysis actually of their risk of mortality after fracture risk, after a fracture. And what you see, this do this is the months after fracture, and this the relative hazard versus prior to the fracture, and you can see a six-fold increase in mortality three months after the fracture, and it falls down after the first year or so, but you see that it doesn't come back to baseline, so even 10 years out, there's still an increased mortality of people who have had a fracture versus those who have not.

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And sorry to say, that this is for women, but for men the picture is even bleaker. There's about an eightfold increase risk of death after fracture for men, and the line is even higher for the men. So men do worse with fractures. So what about in HIV-infected people? And so it's been clear over the last decade or so that the risk of fracture is higher in HIV-infected people compared to uninfected people, so this is an early study

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that we did in the Mass General cohort, or Mass General database, I should say. Looking at men here, women here on the left, men on the right, and you can see that after about age 40. Can't get my cursor, here we go. After about age 40 in women and after about age 30 in men, there's a higher risk of fracture in the HIV-infected population. This is represented by the yellow line. Compared to the uninfected population, the green line. And you can see that as, with increasing age, the difference between HIV-positive and HIV-negative increases, so you get this HIV by age interaction, which is really important when were talking about what happens to older HIV-infected people.

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Now some of this fracture risk, and a good chunk of it is related to low bone density, and so these are data from a meta-analysis some years ago, where we looked at the cross-sectional studies at the time that compared HIV-infected populations to HIV-negative populations looking at their bone mineral density, and what this showed is that the overall prevalence of osteoporosis in the HIV population was about 15 percent and compared to the uninfected controls there was about a three-and-a-half fold increase risk of osteoporosis in the HIV-infected populations.

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So taking a step back, it's good to think about what the definition is of osteoporosis because this is important when we talk about how we assess osteoporosis and how we treat it.

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And so it's a systemic skeletal disorder characterized by two things. One is low bone mass, and the other

is Microarchitectural deterioration of bone tissue. Now I'm so, well think about those two things, low bone mass and microarchitectural deterioration, and then with a consequent increase in bone fragility and fracture.

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So if you'll look at these two micrographs here, normal bone, this is trabecular spine bone here. What you see is it's nice trabecular bone. It's very well organized, whereas the osteoporotic bone, not only is there less bone there, less trabecular bone, but the bone is not organized at all, and that contributes to its weakness.

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So when we define osteoporosis, we generally use dual energy x-ray absorptiometry. So when we use a definition that was for better or worse agreed upon by the WHO, and that's osteoporosis is a t-score less than or equal to two standard deviations, and this is two standard deviations below someone at their peak bone mass, that is around age 25 or 30. 0steopenia is a t-score between -1.0 and 2.5, and normal t-score greater than -2.

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So the important thing is that there is a nice relationship between BMD and fracture, so about a one and a half to three fold increase in the risk of fracture for each standard deviation decrease in bone mineral density.

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The caveats are shown below, so really the t-score is for older people, so 50 and older for men, postmenopausal women. The z-score in the reference population here is an age-match population. A z-score is used for premenopausal women and men less than 50.

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And really, we really shouldn't be making the diagnosis of osteoporosis in those populations unless there's a fragility fracture. Then the other important thing to think about with BMD, and this gets back to the definition that I was talking to you about before, is that it really only explains about half of fracture risk. So bone mineral density really gets at that bone mass question, but it doesn't really get at the microarchitectural deterioration, and I'll be talking about some other techniques that do a better job at getting at that microarchitectural deterioration. So it explains about half of fracture risk, and so the other half of fracture risk is unexplained, and so this is a challenge for risk prediction. So in HIV, there's really a multi-factorial etiology of low bone density and fracture,

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so you have a complex interaction between host factors and disease factors and antiretroviral factors. So the host factors are really important. So these are traditional risk factors for osteoporosis. So low body weight is important. Drug and alcohol use, as really quitting smoking are very important. Hypogonadism, which is common in HIV-infected populations, and Hepatitis C, and I'll just underline this, so you know in pretty much every study, Hepatitis C is a risk factor for fracture in HIV-infected populations, whether or not it has to do with HCV itself or some of the baggage that goes along with

HCV infection is unclear. It's going to be interesting to see if fracture risk decreases with good treatment for HCV like we have now.

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HIV disease factors are important as well, and then we know that inflammatory cytokines like IL-6 and TLF-alpha have direct effects on osteoclast and osteoblast activity as do viral proteins at least in vitro. Increasing bone resorption, that's osteoclast activity. Decreasing bone formation. The medications play a big role, and so you all know that Tenofovir, in the form of TDF is important, it has important independent effects on bone, and we'll be talking more about that. Certain protease inhibitors, so both the currently used protease inhibitors have an effect on BMD that's probably independent, so Darunavir and Atazanavir. And then interestingly enough, with antiretroviral initiation, pretty much regardless of the regimen that is used, there's a loss of bone mineral density,

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and we usually think of antiretroviral therapy being a good thing for health, so testosterone levels increase, lean mass increases, all those things should be good for the bone, inflammatory cytokines decrease, but for bone it's not such a good thing, so it's about a two to six percent decrease. The effect pretty much, it peaks at about 48 weeks, but you don't get recovery, and it stays pretty consistently low thereafter.

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And so two to six percent, you might be thinking is this a lot or is this a little? Should I be worried about this, and so if you look at

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a population that has significant bone loss, and that we think is clinically significant, and you compare the magnitude of the change, so this is healthy women, and so this is stratified by age, and I draw your attention to the second bar on each of these graphs, which is 50-59 during the menopause years, so this is the 2 year percent change in BMD. It's about two percent of the lumbar spine, about one percent of the total body, so what we can say is that the loss is at least equal to about Another population that loses bone that we think is clinically significant

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are people getting glucocorticoids. This comes from the Actonel package insert actually, and not so much what happens with Actonel, but what happens in the placebo group. With the initiation of glucocorticoids, you can see about a three percent annual loss of BMD in that placebo group, so it's similar in magnitude to what you see with glucocorticoids.

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So what can we do to prevent this bone loss in HIV-infected people starting antiretroviral therapy? So the first is avoiding TDF, and so, and these studies have been done looking at TDF versus other nuke regimens or other regimens in general compared to Abacavir compared to Tenofovir alafenamide to Maraviroc to nuke-sparing regimens.

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There's an effect of being off of TDF. Avoiding protease inhibitors is probably a good strategy, so avoid, and most of the comparisons have been with integrase inhibitors or Efavirenz.

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What else could we potentially do? One is to start at the higher CD4 cell count, and I'm waiting for an analysis of the STAR study

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to show that this is indeed true, but we've shown in a combined analysis of ACTG studies that the bone loss, there's a significant greater bone loss if the person starts an earlier, lower CD4 cell count, so you can see especially in that less than 50 group that there's about, there's almost a 2.3 percent decrease greater decrease in that population compared to the greater than 500 group. So what else can we potentially do to decrease bone loss with antiretroviral initiation?

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Now one thing that's pretty low tech and cheap is calcium and vitamin D, and so we did a study looking at people initiating Tenofovir, FTC, and Efavirenz, 00:13:41,370 --> 00:13:43,802 and they were either randomized to vitamin D, D3, 4000 international units a day, or calcium, 1000 milligrams a day, and we followed them over 48 weeks, and you can see here the primary results, and this is the placebo group in red, and the vitamin D/Calcium group here in blue, and you can see that there was still bone loss in the vitamin D/calcium group in both arms that was statistically significant,

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but the effect was about half of what you saw in the placebo group, so at least with the calcium and at least with the Tenofovir, FTC, and Efavirenz, calcium and vitamin D seems to be effective in attenuating but not eliminating the bone loss that you see. Now another strategy is to give a bone medication right before starting antiretroviral therapy,

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so one of the strategies to treat osteoporosis, which I'll be talking about in a little bit is a bisphosphonate, which is as you all know, they're very potent antiresorptive agents, and one of the IV preparations, zoledronic acid is given once a year for the purposes of osteoporosis, and so there was a study that was presented at CROI last year and subsequently published in CID, but it took people initiating antiretroviral therapy

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and gave them a single dose of zoledronic acid to see, versus placebo, to see what happens with their bones, and so if you look in the placebo group, and you can see the lumbar spine changes. There's about a four and half percent drop in BMD in the placebo group, but that loss of bone is completely attenuated and eliminated in those people who get zoledronic acid.

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So this is an attractive strategy to attenuate the bone loss. There are issues, and I'll be talking about issues with zoledronic acid, so in my opinion, and this might come up in other setting in your post test question, (laughs) in my opinion, it's really best reserved for people who have osteoporosis at baseline,

and so similar to what you would do say with a transplant patient, you'd evaluate their bone mineral density and start people on bisphosphonates. Here if someone, especially someone who's at risk for osteoporosis by virtue of their age should get a screening DEXA, and say a someone, a postmenopausal woman or a man greater than 50, who's starting antiretroviral therapy, and if they do have bone loss and definitely osteoporosis, perhaps advanced osteopenia too, I think zoledronic acid was a great way to prevent this bone loss.

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So other management issues regarding bone health in ART-treated patients. So when to screen, how to monitor, when to switch antiretroviral therapy, and when to start bisphosphonates are all big issues.

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So here's a case from my clinic.I have a clinic that is devoted to lipodystrophy, so this guy came in for body fat changes. He was diagnosed with HIV a long time ago, very low CD4 cell count, and had significant exposure to all kinds of antiretrovirals. He, at the time when I saw him, he was on Tenofovir, FTC, and Efavirenz. He also has hypogonadism on transdermal testosterone and has COPD, multiple steroid courses as a result. No history of fracture, and no height loss.

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So the question comes up is whether this guy should be screened for osteoporosis, and so it's always useful to go back to the guidelines of the country that you're talking about, in this case, the U.S., and so this is

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the National Osteoporosis Foundation guidelines. So screen those with a fragility fracture, women 65 and older, men 70 or older. In younger postmenopausal women and men 50 to 69 with clinical risk factors for fracture, and then there are a couple other conditions like rheumatoid arthritis or glucocorticoids where people should get screened as well, and for a long time, when you look at that NOF document to see what are the risk factors that would prompt you to screen someone who is postmenopausal woman not 65 or a man between 50 and 70, HIV or antiretroviral therapy was not among them, but in the last couple years, that's been rectified, and that's actually on the list, so you should be able to get the screening covered. And this has been picked up in various screening recommendations, and so, here is the NOF guidelines that we talked about. Here are the IDSA guidelines.

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Here is a consensus statement that we published a few years ago. Here are the European AIDS guidelines, IDSA guidelines, and this is sort of the most recent is these guidelines that we published in CID last year

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Looking that recommended screening for people with a history, HIV-infected people with a history of fragility fracture, glucocorticoid use, high risk of falls, who, and postmenopausal women and men 50 and older, and then what we do for younger people just to have people think about their bones is to use FRAX, and we'll be talking about FRAX.

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This is a way to assess someone's ten year risk of having a fracture, and you can use it with or without bone mineral density. And so here's the FRAX questionnaire. Show of hands, how many people have used FRAX in practice.

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Okay, so half or so. So this is similar to Framingham risk score for cardiovascular disease. So if you google FRAX, you come up to this website in Sheffield, England, and you pick out your population, so the ethnicity of your, your country, and your, the ethnicity of your population, and you fill in these variables, so you can see them here, and then you press calculate, and you get a 10 year risk of fracture,

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and so for this guy, here are his DEXA results. So you can see that his spine t-score is -2.2, femoral neck is -2.2, total hip is -2.3, so if you go back to the WHO definition for all three sites, he falls into the osteopenic range, so he's not quite in the osteoporotic range.

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What do we do now? So the first thing you need to do is before we label him as osteoporotic or osteopenic, what we need to do is evaluate and rule out secondary causes of low bone mineral density.

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And so here is my typical secondary workup. So vitamin D deficiency, hyperparathyroidism, subclinical hyperthyroidism, hypogonadism, and phosphate wasting, in particular people who are on Tenofovir, where there's an increase prevalence of phosphate wasting, and then these other things in white are things that I do if there are other clinical indications that there may be a problem, so someone who has kidney stones, definitely look for hypercalciuria, someone with GI problems, celiac sprue, et cetera.

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So I draw your attention to two of these secondary causes, and I write low bone mineral density for a reason. I'm not writing osteoporosis because there are two, there are a bunch of reasons for this condition but two that are commonly seen in our population. One is severe vitamin D deficiency, and the second is phosphate wasting.

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And the importance here is that the low bone mineral density that you see in these patients may not be osteoporosis at all but may be osteomalacia. So what's osteomalacia?

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So this is impaired bone mineralization. The collagen matrix is fine, but the calcium phosphate crystals that mineralize the bone are not there. And so with this osteomalacic condition you can get weakness and fracture and pain and anorexia and weight loss, so it can be sort of a subtle diagnosis, but it's something that you should be thinking about in a patient with low bone mineral density, and particularly one that's on TDF. So the important thing is that in the case of severe vitamin D deficiency, and I'm talking single digit vitamin D levels, very high PTH levels, high alkaline phosphatase levels. It's treated with vitamin D to replace and then calcium to remineralize. In the case of phosphate wasting, it's

treated with those things as well as phosphate, and if the patient's on TDF, to switch them off. The other important thing, and this is why I call it the most important differential diagnosis

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for low BMD is that bisphosphonates, at least theoretically, impair bone mineralization, so they actually can make this problem worse. So before if you get a DEXA scan, and the person has osteopenia or osteoporosis, before you jump for the bisphosphonate, you think about osteomalacia, and so you really can't tell if the person has osteoporosis just on the t-score until you've ruled out osteomalacia. Now the best way to rule out osteomalacia is a bone biopsy, but typically we don't do that unless there's a, it's a confusing case.

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So assuming this person has normal secondary workup, and he's in the osteopenia range, so when, who do we treat? And so we treat people who have a hip or vertebral fracture. We treat people that are in the osteoporotic range in general, and for those that are in this ostepenia range, this is where, in the U.S., this is where we rely on FRAX. So you put their numbers into the FRAX calculator, and if they have a 10 year hip fracture probability of greater or equal to three percent or an all osteoporosis related fracture greater or equal to 20 percent, then that person would be eligible to be treated.

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And so here's our FRAX calculator. You put this guy's data in, and you can see that even though he's in the osteopenic range, his major, risk of major osteoporotic fracture is 18 percent, so not quite at that 20 percent threshold, but his risk of hip fracture is 4.1, so greater than that three percent threshold, so he would be eligible for treatment.

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So one thing about FRAX that's come out, it was presented at CROI, year before last, and subsequently published a few months ago, is that there is, that FRAX tends to underestimate true fracture risk in HIV-infected patients.

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Similar to the way Framingham underestimates cardiovascular disease risk in HIV-infected patients and so here you see the, this is in a big VA database, so observed fractures, and so you can see that there's a difference between HIV-positive in red and HIV-negative in green, both major osteoporotic fractures and hip fracture. And you can see that when you estimate fractures by modified FRAX, and it says modified here because they didn't have a family history of hip fracture to do the calculation, but you can see that although they're different because it's a large dataset, the differences between the green and the red are much smaller when you estimate fractures by FRAX.

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So here is the main data, and this looks at the observed versus expected fracture risk. So you can see observed risk of fracture here on the y-axis. The predicted or expected risk here on the x-axis. And what you'll see is that the observed over expected is about 29 percent higher in the uninfected population, so even in the uninfected population, FRAX isn't working well, but here you see that the magnitude of observed over expected is 62 percent. There's more observed fractures than were expected or

predicted, and if you put in, so one of the variables that you can put in in FRAX is secondary osteoporosis, and if you toggle that to yes, it comes down to the observed, expected comes down to where the HIV uninfected people are.

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Now the important thing about the secondary causes is that it really only works when you use FRAX without BMD, so it assumes that the secondary causes that you're talking about lead to increased risk of fracture through low BMD, so it's important, really if you're using it without BMD. So FRAX may, even though it's a good tool, it may underestimate risk in HIV-infected patients.

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So what do we do for someone with osteoporosis Our general recommendations are calcium and vitamin D supplementation. And so typically, I will check the vitamin D level in a patient with osteoporosis and try to get them up into the 30 to 50 range. Calcium, I try to get them the recommendations between 1,000 and 1,200 milligrams of calcium. There's some increasing data, emerging data about calcium supplementation and heart disease.

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There doesn't seem to be true for calcium, dietary calcium, so the party line is to get up to that 1,000 to 1,200 milligrams of calcium, you should be trying to push the dietary calcium as much as you can, and then supplement the rest as needed. So smoking cessation and alcohol reduction are important. Weight-bearing exercise. Part of that discrepancy between what the DEXA, only predicting 50 percent of the risk has to do with fall risk, so over 90 percent of fractures happen when people fall, so if we can keep people on their feet, we can prevent fractures, and so assessing fall risk is really important, and this is I think a really nice question that I use in clinic to sort of open the discussion about falls with patients and ask them if they're worried about falling because patients who are worried about falling, it turns out, are at higher risk of falling because they've already tried to adapt, so they to keep them on their feet,

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and the important reason that you want to identify people is that you can refer them to physical therapy for strength and balance training to keep them on their feet.

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So the pharmacologic therapy, the first line are bisphosphonates. For women, you can use selective estrogen receptor modulators for people who can't take bisphosphonates. Estrogen in women who are also having hot flashes, and then our only anabolic agent is a PTH analogue, teriparatide.

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So bisphosphonates have been investigated in HIV-infected populations, not in terms of reduction in fraction but looking at BMD. The studies haven't been big enough or long enough to look at fracture. They increase BMD to a similar extent in HIV-infected populations compared to uninfected populations. In the general population, they, bisphosphonates generally reduce fracture risk by about 25 to 50 percent, so they have a potent effect on decreasing fractures. Now there's some issues with bisphosphonates that have been widely discussed.

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So I'll talk about these four different bisphosphonates, Alendronate, Risedronate, Ibandronate, and Zoledronic acid. So Alendronate and Risedronate are two oral bisphosphonates that we use quite a bit. They're both generic. Ibandronate, this is Boniva. This is the Sally Field one, which is sort of a weak bisphosphonate, and I almost never use it. And zoledronic acid, or zoledronate is, and this is the one that was used in the initiation trial that I described earlier, is an IV bisphosphonate. That is expensive now, but I think comes off patent next year. And so the issues with oral bisphosphonates are compliance is a real problem,

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so even in post-menopausal women where compliance is generally very good about half the people who start on bisphosphonates aren't on it a year later even though the provider thinks that they're on the bisphosphonate. So this is a real problem and other problems with oral bisphosphonates are GI side effects, somewhere in the 15 to 20 percent range.

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You can get around this compliance problem with a single dose of zoledronate acid, you know, given yearly doses IV. All bisphosphonates have this issue with over suppression of bone turnover, so bisphosphonates are very potent inhibitors of the osteoclasts, and it's thought that prolonged inhibition of the osteoclasts has some untoward effects that are really very rare, and one of them is osteonecrosis of the jaw, and the other is atypical femoral fractures, and generally these are patients who are on bisphosphonates for five, 10 years plus. And fortunately these are events in the five to 10 in 100 thousand people, so really quite low,

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but the concerning thing I think is that a lot of people aren't getting bisphosphonates that need to be on bisphosphonates, and a lot of people have stopped bisphosphonates that should be on. Clearly there was a period about 10 years ago, or 15 years ago, that bisphosphonates were probably overused, but now there's emerging data that bisphosphonates are generally underused because of concerns about these problems. They're important, very important drugs for the prevention of osteoporotic fracture, and because of these very low risk side effects, the osteonecrosis of the jaw and the atypical femoral fractures, there's recommendations for people to take a bisphosphonate holiday,

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and so generally it's after five years or so, in moderate risk and low risk people that they should take a holiday form bisphosphonates, and this is generally the moderate risk are people who have, don't have osteoporosis, but even people in my mind, people who have mild osteoporosis could potentially get a drug holiday for, and typically I monitor with bone mineral density and look for drops in BMD. There's a lot of questions about this holiday period, and all this McClung article is a very good one, but it's all based on expert opinion

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and not much evidence, and there's still a lot of questions regarding how long people should be on get a holiday, how to monitor them, is bone mineral density the best way to monitor them, how often should you do a bone mineral density test, can you use markers of bone turnover, what medications to do after

the holiday, so if you have stopped bisphosphonates do you do something else, if you deem that the patient needs to go back on some sort of bone protective regimen, so all these questions are really unanswered. So one thing with this guy is that he's on TDF, and so the question comes up, do we switch him off of TDF.

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And so this is again from these guidelines we did in CID, and for people who for previous ART therapy, so we're down here, if they're on Tenofovir, TDF, switching them to a Abacavir or Raltegravir or a non-TDF regimen would be advisable. And so here's, there's actually quite limited data of people switching from TDF to Abacavir.

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This is one small study called OsteoTDF that was done in Spain, and you can see sort of this is the, down here is the continue on Tenofovir. This is people who have low bone mineral density on TDF. Either to continue on, they continued on their TDF or they were switch to Abacavir with the same third drug regimen, and you see a greater increase in the Abacavir group compared to those who continued on Tenofovir, although the between group change was not statistically significant, and this was a very small study, so you can see 26 subjects, and you can see lumbar spine, so again those who were on TDF had a greater loss in BMD compared to those who were switched to Abacavir, but that the between group was not statistically significant.

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So suggestive that Abacavir may be helpful here, but really not great evidence. So another thing to do would be to take out the nuke, and this is people switching from TDF to Raltegravir, and with osteopenia, and this is a single arm study from Australia, and you saw pretty big increases in BMD at 48 weeks, so three percent at the spine, 2.5 percent at the hip doing that substitution, so that's a possibility if it's okay from an antiretroviral standpoint.

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Another possibility is to switch from TDF to TAF, so the new preparation of Tenofovir, Tenofovir Prodrug, and so this is a study which looked at patients who had some degree of renal dysfunction. It turns out they had a higher prevalence of osteoporosis and osteopenia as well, and so what you see is that in the spine, there was about a two percent, a 1.9 percent increase in BMD over 48 weeks, and about one percent at the hip, so this is a viable option as well.

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There're other more risky things that you could potentially do that I don't, I'm an endocrinologist. I don't treat HIV, but in Europe, I know that monotherapy is something that some people think might be a good option so this, the patient on two nukes and boosted Atazanavir, were either kept on the same regimen or the two nukes were just taken off. And so a little risky, and they had quite a few drug failures in this study, but there was beneficial effects on bone.

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So what do we do as far as monitoring goes? Here for people who are on bisphosphonates, repeating a DEXA in two years. This is sort of the recommendation, and I often repeat in one year. I think it helps.

You know, I mentioned the fact that compliance can be a big issue, and if you can get a test to show that the patient's bone mineral density is improving, it tends to, I think it helps compliance for the patient. And then for people who have advanced osteopenia, they should do one or two years, so this is a t-score between -2 and -4.9, and five years if they have very mild osteopenia, and these are recommendations that are based really on the general population, so a couple things that I wanted to touch on in the last minutes of the talk, a few issues that have come up in meetings from the fall. One I mentioned that DEXA is a good tool but not a great tool. It doesn't get at this question of bone quality,

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and I want to talk about another modality that's called trabecular bone score, and so this is a indirect measure of bone microstructure, so the higher the score, the better. And so basically what it does is it takes the spine view. If you have a DEXA scan, you're going to a DEXA center that has this software, it's not any extra radiation for the patient. It's not any extra time for the patient, but what it does is it takes the scout films that are done really for positioning, and they're good enough so you can, the computer can do what's called a variogram to look at how much trabecular bone is there and how regular it is.

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So here this is normal BMD on the top slide, and so this is the variogram here, and so you see it's pretty homogenous, the white boxes and the gray boxes are pretty well uniform, and this gives a TBS of 1.36. And as opposed to the osteoporotic bone, so similar to the micrograph that I showed you before, less bone there but unorganized bone, and so you can see with all this unorganized bone that you have, there are differences in the variation of the color of these boxes, some white and quite a few black, and this comes up in the variogram that has a lot more of that red. And so these are the TBS values that are considered normal, so greater than 1.3, 1.35, between 1.2 and 1.35 is intermediate, then you have degraded, less than -2.

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And so the other thing that's important with the TBS is that you can add it to the FRAX equation to give more precision to your 10 year estimate of risk, so what this means is that the TBS is providing information independent of these other risk factors, including bone mineral density, so conventional bone mineral density, and so the TBS data in HIV-infected people is coming out,

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so this was the data from the WIHS cohort, so this, some of you may know, this is a cohort of HIV-infected and uninfected women from right now I think it's nine sites in the U.S. And so this looked at, there's a metabolic substudy of 215 women with two or more TBS measurements, and this is the lumbar spine BMD, so you can see it's lower in HIV positive. Somehow I lost that this was a big bar before. But this is the more important thing where you can see that the proportion of people who are the women who are HIV positive, who have intermediate TBS or degraded TBS is higher for HIV positive versus HIV negative, and so, the flipside of this is the odds ratio of normal TBS was 62 percent lower in the HIV-infected group.

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So what this study suggests is that not only is bone mineral density lower, and this is what you'd see on

the panel on the left, but the bone architecture is abnormal as well in HIV-infected, at least a population of HIV-infected women.

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Another TBS study was presented. Now this actually was in New York here at the comorbidities meeting in September, and this is a cohort from Dublin called UPBEAT, and so it's 474 HIV positive and HIV negative, and what they looked at is TBS and in a univariate analysis, the TBS was lower in the HIV infected group compared to HIV uninfected, and they added a bunch of different risk factors into the model, and interestingly enough, the difference between HIV positive and HIV negative became non-significant when they added in smoking into the model.

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Suggesting that smoking is also having an effect on bone quality and maybe mediating this difference that you see, at least in this population between HIV positive and HIV negative, and we know from FRAX that smoking is one of these things that we put in 'cause it's not, the effect of smoking on fracture is not mediated through BMD, so maybe it's mediated through this decrease in bone architecture. So the other test that I want to talk about is something called bone material strength or osteoprobe or reference point indentation.

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And this is a minimally invasive technique where a probe is placed on the anterior shin and the area's numbed up, and the, you get through the periosteum, and it makes a microindentation, and the depth of the microindentation is proportional to the reductionin bone quality, and

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this appears to be at least in preliminary studies to provide information independent of BMD, and actually we're training to do this. I went to Mayo Clinic yesterday to train to do this for

a study that I'm doing, and I had it done yesterday. I'm still walking, no limp. (laughs)

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It doesn't feel like anything really, and it's interesting in that it provides some complementary information, so here you see the pit that it makes in the surface of the bone, and these are the natural occurring sort of features, and it's about a 300 micrometer little indentation, and so you can see in this study from Spain that the control population had much higher bone material strength compared to the HIV-infected population, and this is true even after adjustment for sex, age, body mass index, vitamin D, CRP, and fibrinogen.

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So I think that this is an interesting tool. Right now a research tool, but potentially could be used for clinical assessment as well.

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So the other hot topic in bone research I want to talk about is PrEP, and so we know that PrEP is effective, and if used and if adhered to, but we know that TDF has effects on bone. And so I want to bring your attention to a couple studies that were at the Co-Morbidities workshop a few months ago.

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This one is an extension of an adolescent study, so ATN 110, and so this is the multicenter study in very high risk population of young people, so people that hadn't reached their peak bone mass yet, so between 18 and 22 MSMs, and you can see quite a few seroconversions in this group, and so what they did in this extension study is they took people who in this initial 48 weeks of this study lost bone.

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And then they asked the question well what happens when we take PrEP away what happens to the bones. In this population, so first of all, there were quite a few, with this population of 102, quite a few seroconversions, suggesting again that this is quite a high risk population. It came down to, after some of these other exclusions, it came down to 72 people, who were in this bone extension analysis. And so I'll walk you through these slides,

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which I think are pretty interesting. And so what you see is as we see in other studies, a drop in BMD in the first 24 weeks, at both the hip, spine, and the whole body and a little bit of rebound at the spine and further decrease at the hip, and leveling out at the whole body, and then once people stop the TDF/FTC PrEP, you see rebounding, so rebounding in spine BMD and back up to baseline at the, for the whole body and the hip,

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so they analyzed the data in another way. They looked at the z-score instead of just the percentage changed, and as I mentioned earlier, the z-score is the number of standard deviations away from an age-matched population, and so there are a few things to note about this graph here on the right.

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The first is that at baseline, the BMD in this MSM population is really quite low, and so typically a normal BMD should be zero, but BMD here is somewhere between - 3 and -5, - .3 and -.5, so a third to a half a standard deviation lower than you might expect, and this actually we have seen in other PrEP studies, and we see in a study with primary HIV infection where there's not enough time for anything to happen in the bone once they're affected. So there's something that we don't understand about MSM and low bone density. So we'll follow this up, and we'll look at the changes in the z-score over time, over these 48 weeks and then what happens when they come off of TDF. And what you see is at the hip, is that you have a decrease in BMD and then it pretty much comes back to baseline, the baseline z-score. For the total body and the spine, a little bit different, and so you have an improvement in BMD, but by the end at 48 weeks, it's still lower, the BMD is still lower than baseline, so even though you see this big percentage change because they're getting, they're two years older, they should actually have a higher BMD than is expected,

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so what this suggests is that perhaps the insult of Tenofovir or FTC on the bone does not really completely revert at least after 48 weeks in this population who hasn't reached their peak bone mass.

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The other PrEP study that I want to bring your attention to is a demonstration project from Australia,

where they took about 50 MSM, and looked at their BMD with PrEP, and they're a very adherent population, and it's a little older population, 34 years, and the decrease in BMD that they saw was more than what you, what has been seen in some of the randomized trials for PrEP, such as iPrEx, and the CDC study, and this might, is probably related to their high degree of adherence, so there were quite a few people who had a quite significant bone loss. 53 percent had either a five percent loss at either the spine or the hip. Now the degree to which this is reversible over time is not clear.

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So concluding, fractures are likely to be a major source of morbidity and mortality for aging HIV-infected patients. The etiology is multifactorial, so protease inhibitors and TDF have independent detrimental effects on bone. Switching off of these medications is recommended for those who are at increased risk of fracture, so DEXA screenings should be more aggressive in HIV-infected people. Monitoring is really by DEXA and FRAX if you're don't have DEXA available. And the treatment guidelines for osteoporosis really should follow those established in the general population. So thanks for attention and happy to take questions.

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(applause) [END Presentation]